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Review

Brugada Syndrome: Channelopathy and/or Cardiomyopathy

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Abstract: Brugada syndrome (BrS) has been traditionally considered a pure electrical disorder without an underlying structural substrate. However, early ECG studies showed the presence of depolarization abnormalities in this condition, while many studies based on advanced imaging have suggested the presence of subtle structural alterations. On the other hand, electrophysiological study (EPS) and electroanatomic mapping (EAM) techniques have provided important data regarding right ventricular functional and structural arrhythmic substrate. More recently, histology and immunology shed light on the possible role of fibrotic and inflammatory substrates in BrS. Notably, a significant overlap between electro anatomical and structural features in BrS and arrhythmogenic cardiomyopathy has been proposed. In this review, we summarized the physio pathological pathways and substrate underlying BrS. A deeper knowledge of the structural abnormalities involved in the pathogenesis of this disease could improve our diagnostic and prognostic approach, while novel findings regarding the role of inflammation and immune activation could potentially lead to new therapeutic strategies for BrS.

Keywords: Brugada syndrome; ECG; advanced imaging; electrophysiology

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1. Introduction

Brugada syndrome (BrS) is an inherited arrhythmic condition associated with a typical ECG pattern and increased sudden cardiac death (SCD) risk [1–3]. The type 1 ECG pattern is defined as an elevation of the J point with coved morphology in V1 and/or V2 lead in second, third or fourth intercostal spaces [1–4]. The pattern can be spontaneous or induced by drugs blocking the sodium channels. BrS has been traditionally considered a pure electrical disorder characterized by repolarization abnormalities without any underlying structural substrate [1,2,5,6]. The first genetic variant in the Sodium Voltage-Gated Channel Alpha Subunit 5 (*SCN5A*, *OMIM * 600163*) gene was discovered in 1998 [7]. Since then, hundreds of variants in the *SCN5A* gene have been discovered with an autosomal dominance inheritance pattern occurring in approximately 30% of cases [8]. However, the clinical significance of many *SCN5A* variants have been questioned following the criteria established by the American College of Medical Genetics [9]. Variants in other genes (*CACNA1C*, *OMIM * 114205*, *GPD1L*, *OMIM * 611778*, *HEY2*, *OMIM * 604674*, *PKP2*, *OMIM * 602861*, *RANGRF*, *OMIM * 607954*, *SCN10A*, *OMIM * 604427*, *SCN1B*, *OMIM * 600235*, *SCN2B*, *OMIM * 601327*, *SCN3B*, *OMIM * 608214*, *SLMAP*, *OMIM * 602701*, and *TRPM4*, *OMIM * 606936*) have been reported as potentially pathogenetic in the literature,

but according to current diagnostic guidelines and recommendations, only pathogenic *SCN5A* variants should be considered causative of BrS [2]. Patients with pathogenetic variants in the SCN5A gene without arrhythmias or pathological findings at advanced imaging represent a gray area that should be appropriately addressed in future studies. Notably, genotype–phenotype correlation remains elusive in this population, and the prognostic role of these variants is still unclear.

Interestingly, both loss- and gain-of-function *SCN5A* variants have also been associated with dilated and arrhythmogenic cardiomyopathies (AC) [10,11]. Loss-of-function variants have been associated with BrS and sick sinus syndrome, while gain-of-function mutations can determine multifocal ectopic premature Purkinje-related complexes syndrome.

Electroanatomic mapping (EAM) studies, due to the high sensitivity in detecting subtle pathological alterations, have demonstrated the presence of pathological voltages in the right ventricular outflow tract (RVOT) in patients with BrS [2,12,13]. In addition, pathology studies showed the presence of fibrosis and inflammation in tissue samples obtained from RVOT by autopsy or endomyocardial biopsy (EMB) [14–16]. More recently, novel echocardiographic and cardiac magnetic resonance (CMR) tools demonstrated the presence of structural and functional RVOT abnormalities [17,18]. Notably, many similarities in terms of molecular and cellular phenotype have emerged between BrS and AC [19,20].

This review aims to provide a comprehensive overview of the evolving understanding of BrS pathophysiology, discussing the implications for diagnosis, risk stratification, and treatment. Potential future perspectives to improve the management of BrS patients are also explored.

2. Electrocardiography and Invasive Electrophysiology: A Complex Interaction of Repolarization and Depolarization Abnormalities

The diagnosis of BrS is based on the recognition of a spontaneous type 1 pattern (either on conventional or high right precordial leads) with high take-off ST segment elevation > 2 mm and coved morphology irrespective of the presence of symptoms [2,4,21]. Notably, many cardiac diseases (including myocarditis, pericarditis, infarction, pulmonary embolism, hyperkalemia, hypercalcemia, AC, and hypothermia) could potentially determine ECG abnormalities mimicking Brugada pattern [21]. Differential diagnosis could represent a significant challenge, since some of these disorders (such as AC) could share some pathophysiologic pathways with BrS.

The ECG pattern can be dynamic with variations during fever or alcohol consumption [2,22]. In case of patterns induced by sodium channel blockers (by ajmaline, flecainide, procainamide or pilsicainide infusion) type 1 pattern, additional ECG, family history, and clinical and genetic criteria are needed to diagnose BrS [2,23]. Early studies focused on the peculiar repolarization abnormalities leading to the postulation of the "repolarization" theory based on the imbalance between reduced Na+ currents and preserved transient outward potassium (Ito K) currents. This mismatch, due to the inhomogeneous distribution of the Ito between the epicardial and endocardial layers, could therefore determine a transmural voltage gradient leading to the diagnostic ECG pattern [24–26]. This phenomenon was also thought to be the basis for phase 2 re-entry mechanisms and ventricular arrhythmias.

Multiple works showed that the presence of spontaneous type 1 ECG pattern determines an increased arrhythmic risk [27,28]. The presence of early repolarization (ER), ST segment elevation, and even coved patterns in the inferolateral ECG leads can occur in BrS patients, and they could be associated with a more serious phenotype [29–31]. Kawata et al. showed that in some BrS patients with inferolateral ER pattern, VF onset was shortly preceded by multiple premature ventricular contractions originating from the left inferolateral wall [31]. These observations could suggest more extensive biventricular involvement rather than classical RVOT abnormalities.

The maximal interval between the T wave peak and end and its dispersion could potentially be associated with worse outcomes in BrS subjects [32]. Increased repolarization time dispersion and marked repolarization gradients (revealed by steep epicardial J waves) have been demonstrated in BrS during electrophysiological study (EPS) studies [33]. Moreover, T wave alternans during sodium channel blocker administration could be a marker of electrical instability and increased arrhythmic risk [34].

However, since the early 2000s, many studies have focused on the presence and significance of depolarization abnormalities in BrS patients. Ikeda et al. demonstrated a high prevalence of late potentials (LPs) with an association with worse outcomes by using signal-averaged ECG (SA-ECG) in BrS subjects [35]. Similarly, an increased QRS duration is independently associated with adverse arrhythmic events at follow-up [36,37]. Other authors demonstrated that the presence of fragmented QRS (f-QRS) at standard 12-leads and filtered high cut-off frequency ECG is associated with spontaneous ventricular fibrillation (VF) at follow-up (Figure 1) [38,39]. On the other hand, the presence of preserved HV intervals at EPS in many patients suggested the presence of a primary RV conduction delay [35]. Of note, Morita et al. were able to show in a canine RV tissue model of BrS that delayed epicardial activation reproduced similar f-QRS features along the myocardial layers, suggesting a possible pathogenetic mechanism [38]. Prominent R waves in aVR lead, an indirect marker of RV conduction delay, represent a negative prognostic marker in BrS patients [40]. The presence of deep S waves in leads I, II, and III, atrial fibrillation onset, and the Tzou criteria (V1R > 0.15 mV, V6S > 0.15 mV, and V6S: R > 0.2) have also been associated with ventricular arrhythmias at follow-up [41,42]. These ECG features provide additional evidence of delayed RVOT activation in BrS patients.

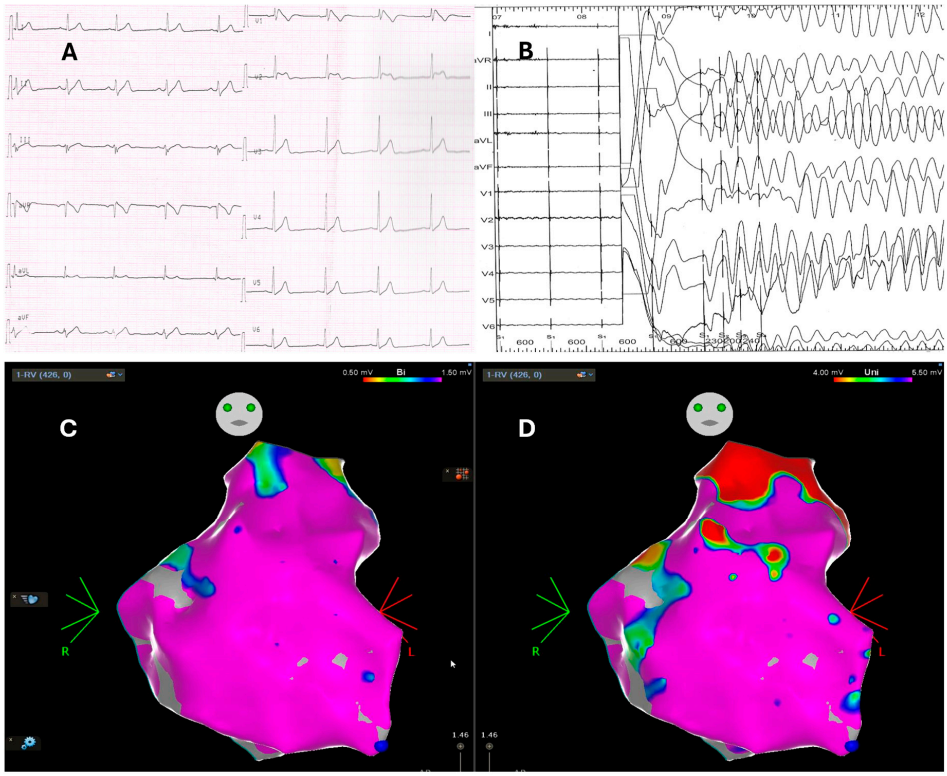

Figure 1. (**A**): ECG of 50-year-old patient with spontaneous type 1 BrS and fragmented QRS complexes in inferior leads [27,28,38,39]. (**B**): During EPS, a rapid polymorphic VT was induced after a single extra stimulus, necessitating external defibrillation. The patient underwent transvenous ICD implantation [27,41,43]. (**C**,**D**): Abnormal voltages were detected at unipolar mapping (**D**), without significant pathological signals at bipolar map (**C**) [13,16,44]. BrS; Brugada syndrome; EPS; electrophysiological study; ICD, implanted cardioverter defibrillator.

The presence of atrioventricular (AV) conduction disorders and increased HV interval in BrS patients (Figure 2) [45,46] have been respectively demonstrated in ECG and EPS studies. Moreover, atrioventricular and intraventricular conduction disorders (namely right bundle branch block and first-degree AV block) have been associated with malignant arrhythmias at follow-up, while RVOT depolarization abnormalities have been detected in many EPS studies, even by use of isochronal activation mapping [12,13,47–49]. More recently, Rossi et al. demonstrated that increased difference in the RV refractory period between RVOT and RV apex (expressed as ΔRPRVOT-apex > 60 ms) was independently related to adverse clinical events over conventional clinical risk factors and VT/VF inducibility at EPS [50].

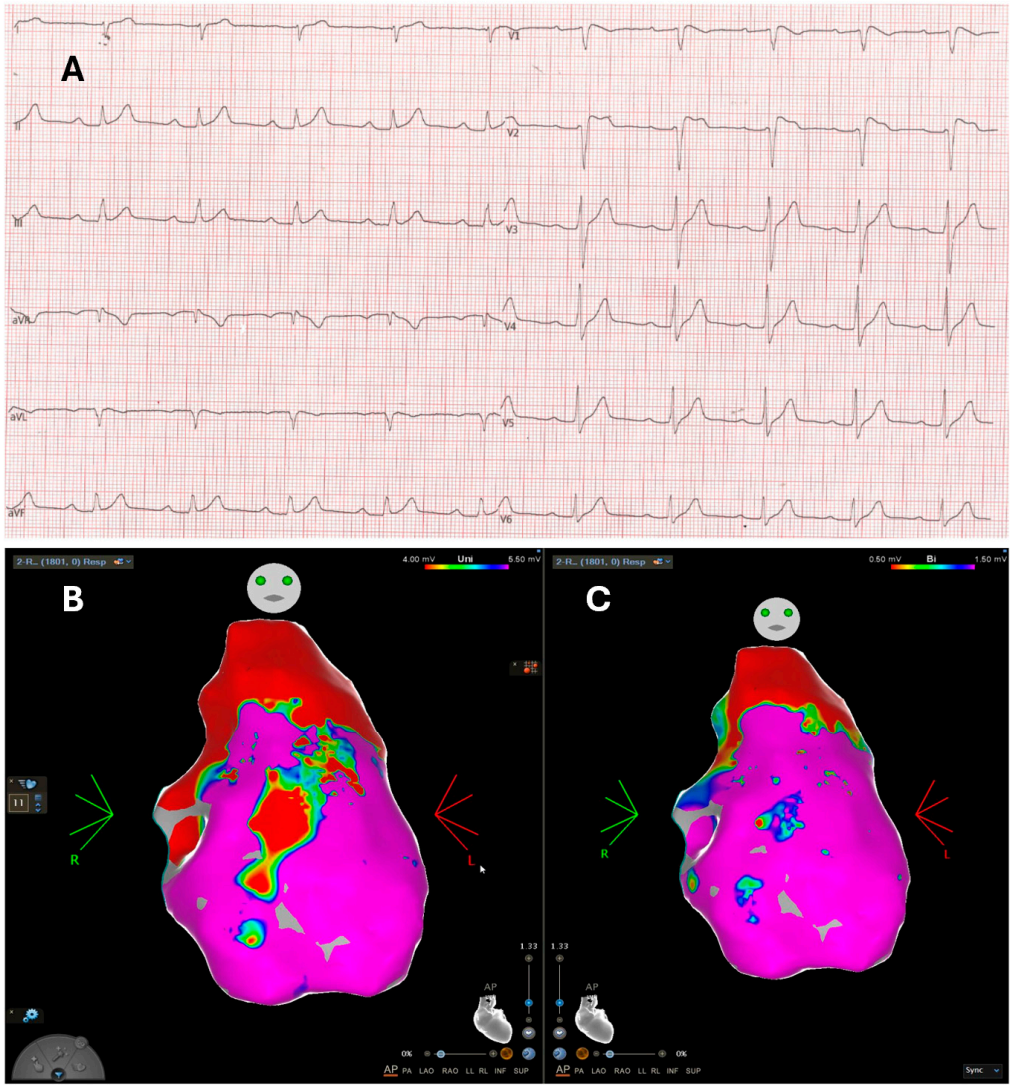

Figure 2. (**A**): ECG of 30-year-old male presenting spontaneous type 1 BrS pattern, first degree AV block, and rightward axis deviation [27,28,48,49]. (**B**): Unipolar electroanatomic mapping demonstrated the presence of pathological voltages in the anterior RVOT. (**C**): Presence of abnormal voltages in bipolar mapping [13,16,44]. BrS, Brugada syndrome; AV, atrioventricular; RVOT, right ventricular outflow tract.

Taken together, these studies suggest a prominent role of depolarization abnormalities mainly located in the RVOT of BrS patients.

3. Electrophysiological Study: The Prognostic Role of Programmed Ventricular Stimulation

Over the years, many studies provided conflicting results regarding the prognostic significance of VT/VF inducibility after programmed ventricular stimulation (PVS) during EPS [27,43,51]. The use of EPS for risk stratification may be considered in BrS patients with low evidence levels according to current European Guidelines [4]. Heterogenous PVS protocols and selection biases in the cohorts could explain these differences. However, structural substrate inhomogeneity could potentially be another implicated factor. A recent large prospective study demonstrated that VF/VT inducibility during EPS was an independent predictor of major events in patients presenting spontaneous type 1 pattern monitoring [27]. Notably, the authors performed serial modified 12-lead Holter monitors to detect latent type 1 pattern in all subjects. In this way, they were able to identify a high-risk subgroup in this population.

4. Multimodality Imaging: Subtle Functional Abnormalities Revealed by Advanced Echocardiography and Cardiac Magnetic Resonance

BrS has been conventionally considered a pure channelopathy with normal biventricular function and structure. Conventional two-dimensional echocardiography did not demonstrate significant left or RV abnormalities in older BrS cohorts. Tissue Doppler and speckle tracking analysis can detect functional abnormalities in many cardiac disorders. Mitroi et al. demonstrated that higher RV index of myocardial performance (RIMP), reduced RVOT shortening, and higher RV mechanical dispersion were significantly associated with arrhythmic events in patients affected by BrS [17]. Interestingly, even impaired LV strain parameters (such as LV mechanical dispersion) have been associated with worse outcomes at follow-up [52]. Three-dimensional echocardiography demonstrated worsened mechanical contraction and reduced right ventricular ejection fraction (RVEF) after ajmaline infusion [53].

CMR, due to its high spatial resolution and the possibility to perform multiplanar sequences and tissue characterization, provided an incremental ability to detect subtle alterations in BrS patients. Early CMR studies showed increased biventricular volumes and reduced RVEF in BrS patients compared to controls, especially in genotype-positive subjects [54,55]. Dedicated CMR sequences demonstrated abnormal RVOT dimensions and contractions in BrS patients [56]. Bastiaenen et al. described the presence of late gadolinium enhancement (LGE) in 8% of BrS patients [57]. Moreover, an increasing prevalence of LGE over repeated CMRs has been described in the literature, suggesting a progressive increase in the substrate underlying BrS [58]. Novel CMR parameters (such as feature tracking analysis) could provide incremental sensitivity for RV dysfunction detection. Pappone et al. demonstrated that reduced RVOT feature tracking (RVOT-FT) was associated with increased pathological voltage mapping areas on the epicardial EAM [18]. Moreover, ajmaline infusion determined further RVOT-FT value reduction in this cohort.

The main ECG, imaging, and EPS features associated with adverse outcomes in BrS are summarized in Table 1.

Table 1. Clinical, genetic, ECG, and imaging characteristics associated with adverse outcomes.

Clinical and Genetic Variables	ECG	Imaging	EPS
Elevates Shanghai score values [23] Family history of SCD [30,41] Unexplained syncope [43,48,49,51,59] Missense *SCN5A* mutations in BrS-enriched domains [59] Polygenic risk score for BrS [59]	Spontaneous type 1 Brugada pattern [27,28,43,48,49,51,59] LPs on SAE-ECG [35,36] Increased QRS duration [37,38] Fragmented QRS [39,40,43] Tpeak to Tend [33,40] Early repolarization pattern in inferolateral leads [30,31,39] Tall R wave in aVR [40] S-wave duration in lead I $\geq$ 40 ms [41] Atrial fibrillation [41] Deep S waves in lead I [42] S in lead II > S in lead III [42] Positive Tzou criteria [42] Atrioventricular block [48,49] TWA during sodium channels blocker infusion [34]	Increased RV index of myocardial performance [17] Reduced RVOT values on STE [17] Increased RVMD on STE [17] Increased LVMD on STE [52] RV dysfunction on three-dimensional echocardiography [53]	VT/VF inducibility during EPS [27,41,43] Reduced RV refractory period [51] Heterogenous RV refractory period [50] Persistence of BrS pattern after RVOT ablation [60]

SCD, sudden cardiac death; BrS, Brugada syndrome; LP, late potential; SAE-ECG, signal-averaged ECG; TWA, T wave alternans; RV, right ventricle; RVOT, right ventricular outflow tract; RVMD, right ventricular mechanical dispersion; LVMD, left ventricular mechanical dispersion; STE, speckle tracking echocardiography; VT, ventricular tachycardia; VF, ventricular fibrillation; EPS, electrophysiological study.

5. Electroanatomic Mapping: Electrical and Structural Substrate Insights

EAM can provide detailed characterization of the myocardium in terms of reduced voltage areas and presence of fragmented signals and LPs. Due to its high sensitivity, it can detect abnormal underlying substrates even in patients without evident abnormalities at CMRs [61,62]. Letsas et al. demonstrated the presence of abnormal EAM voltages in patients with apparently normal CMRs [13]. Notably, more extensive pathological areas were detected at unipolar compared to bipolar mapping, suggesting a more pronounced epicardial substrate. Multiple groups reported higher VF inducibility during EPS in subjects presenting more diffuse pathological areas both at unipolar and bipolar mapping [13,44]. Transcatheter ablation has emerged as a possible therapy for recurrent ventricular arrhythmias in patients with BrS [12,63–65]. The presence of fragmented and delayed potentials and significant pathological voltages in the epicardial layer have been demonstrated in multiple works, with a further increase after sodium channel blocker infusion [63,64]. By targeting the abnormal substrate, a significant reduction in the ECG pattern and VT/VF inducibility at baseline and after ajmaline infusion has been described [12,63–65]. Interestingly, Pieroni et al. described high rates of fibrosis and inflammatory infiltrates (mainly activated T lymphocytes) in BrS with pathological unipolar and bipolar mapping [16]. Patients with edema and lymphocytic infiltrates presented higher rates of VF inducibility during EPS. It is notable that subjects with bipolar mapping abnormalities presented higher prevalence of inflammatory infiltrates, suggesting a strict relationship between transmural involvement and inflammatory activation. More recently, Pappone et al. described a significant worsening of RVEF and RVOT strain during ajmaline infusion [18]. Moreover, the authors reported a corresponding increase in altered unipolar mapping areas with a significant correlation with post-ajmaline RVEF.

Recently, the BRAVO registry provided important data regarding long-term outcomes after RVOT epicardial ablation in BrS [60]. BrS patients undergoing epicardial ablation experienced high event-free survival rates (up to 96% at the 5-year follow-up in the case of repeated procedures). The only variable independently associated with favorable outcomes at follow-up was the absence of Brugada ECG pattern at baseline or after sodium channel blockers after ablation at multivariate analysis. This element reinforces the importance of extensive substrate ablation in this setting. Interestingly, 29% of subjects presented an additional pathological substrate at EAM in the inferior RV epicardium, and three patients presented significant EAM abnormalities in the left posterolateral epicardium associated with the presence of early repolarization pattern.

In a recent study by Cheniti et al., the authors demonstrated the presence of LV EAM abnormalities in BrS patients undergoing epicardial mapping and ablation due to sustained ventricular arrhythmias [66]. Patients with LV substrates presented higher rates of conduction defects, more extensive RV EAM abnormalities, and frequent pathogenetic *SCN5A* variants.

Therefore, we could hypothesize that the presence of pathological EAM voltages in atypical RV and even LV segments could be the expression of subtle diffuse biventricular involvement in BrS.

6. Histology and Immunology: Exploring the Substrate and the Role of the Immune System in the Disease

Coronel et al. in 2005 described the presence of fibrofatty infiltration in the RVOT epicardium of the explanted heart of a BrS patient undergoing heart transplantation after multiple electrical storms [67]. Electrophysiological study of the explanted heart demonstrated conduction delays in the RVOT.

Tissue samples from autopsies and epicardial biopsies obtained during surgical RVOT ablations showed a high prevalence of fibrosis and reduced expression of gap junction protein connexin 43 (Cx43) in BrS patients compared to controls [15]. The authors detected similar histopathological findings from the left ventricular samples. Cx43 has a crucial function in determining correct cellular migration and RVOT zonation, and this evidence could explain the preferential RVOT involvement in BrS. Frustaci et al. performed biventricular angiography and EMBs in a cohort of BrS patients [14]. They detected the presence of microaneurysm and inflammatory infiltrates (activated T lymphocytes) in both ventricles with increased myocyte apoptosis and necrosis.

EAM can detect the presence of interstitial fibrosis at histology compared to CMR in right ventricular cardiomyopathies, as demonstrated by Santangeli et al. [68].

Pieroni et al. performed RVOT EMBs guided by EAM in BrS subjects [16]. Lymphomononuclear infiltrates were detected in 80% of cases together with necrosis, myofibrillar rarefactions, and cytoplasmic vacuolization.

A subsequent study described the presence of autoantibodies against alpha-cardiac actin, alpha-skeletal actin, keratin, and connexin-43 from sera of BrS patients [69]. Moreover, analysis of the tissue samples by autopsy or EMBs demonstrated abnormal a-cardiac actin, a-skeletal actin, keratin, and connexin-43 aggregates. The authors hypothesized that structural abnormalities in the sodium channels could determine inappropriate apoptotic processes leading to exposure of cryptic cardiac epitopes and the consequent activation of the immune system. Identification of circulating autoantibodies and related pathological protein aggregates in the myocardium could therefore potentially represent a possible pathological mechanism. We reviewed the main histopathological studies in Table 2.

Table 2. Histopathological studies in patients with Brugada syndrome.

Study	Population	Design	Pathological Findings	Notes
Coronel et al. [67]	1 BrS patient undergoing heart transplantation due to refractory electrical storm.	Histopathological and electrophysiological evaluation of the explanted heart.	Presence of fibrous and fatty infiltrations in RV and RVOT.	Presence of conduction delay in RVOT at electrophysiological study.
Frustaci et al. [14]	18 BrS patients suffering arrhythmic events.	Biventricular angiography and EMBs.	Activated T lymphocytes and necrosis in 14/18 patients. Myocyte vacuolization and fibrofatty replacement in 3/18 subjects.	Presence of viral genome in 28% of subjects. Evidence of microaneurysm in the RV and LV (7 and 4 subjects, respectively) at angiography.
Nademanee et al. [15]	6 BrS patients suffering SCD and 6 BrS subjects undergoing surgical epicardial RVOT ablation.	Histopathological evaluation of the explanted heart. RVOT mapping and biopsies in patients undergoing surgical ablation.	Increased fibrosis and collagen in the RVOT. Reduced Cx43 expression in BrS patients.	Presence of delayed, prolonged and fragmented QRS on RVOT epicardial electrocardiogram in patients undergoing ablation.
Pieroni et al. [16]	30 BrS patients (37% of them symptomatic).	30 BrS patients underwent EPS and endocardial RV EAM. 20/30 subjects underwent EAM-guided EMB.	Activated T lymphocytes infiltrate in 12/20 subjects and myocyte necrosis in 3 of them. Interstitial fibrosis and replacement necrosis in 15/20 patients.	Patients with inflammation at EMB presented higher rates of VF inducibility and more extensive bipolar abnormalities at EAM.

BrS, Brugada syndrome; RV, right ventricle; RVOT, right ventricular outflow tract; EMB, endomyocardial biopsy; LV, left ventricle: SCD, sudden cardiac death; Cx43, connexin-43; EPS, electrophysiological study; VF, ventricular fibrillation; EAM, electroanatomic mapping.

7. Brugada Syndrome and Arrhythmogenic Cardiomyopathy: A Common Spectrum of Disease

AC is a genetic disorder caused by desmosomal and non-desmosomal genes characterized by biventricular fibrofatty replacement and high rates of ventricular arrhythmias [70–72]. Notably, RVOT structural abnormalities are common and have been included in the revised 2010 diagnostic criteria for RV AC [73,74]. Corrado et al. described a group of patients suffering sudden cardiac death with histological findings compatible with AC and presenting dynamic right anterior ST segment abnormalities diagnostic for BrS [75,76]. Similarly, the presence of epsilon waves has been described in BrS ECG [77]. Since then, growing evidence of structural and functional myocardial alterations in BrS has emerged. Multiple genetic studies described a wide spectrum of diseases caused by *SCN5A* variants, including BrS, long QT syndrome, sick sinus syndrome, AV block, atrial fibrillation, and dilated cardiomyopathy with pronounced arrhythmic burden [10,11,20,78].

The connexome and the intercalated disks provide correct intercellular adhesion and electromechanical coupling to the myocytes [19,20,79,80]. Desmosomes represent the main structure involved in electromechanical connections between cardiomyocytes. Heterozygous nonsense, frameshift, or splicing variants in the *PKP-2* gene (expressing a protein of the armadillo family) have been associated with RV-dominant AC. PKP and junctional plakoglobin (encoded by *JUP* gene, OMIM * 173325) are strictly con-

nected to desmoglein-2 (*DSG-2* gene, OMIM * 125671) and desmocollin-2 (*DSC-2* gene, OMIM * 125645) proteins in the extracellular space [79]. Interestingly, some authors described a homozygous DSC-2 deletion associated with AC onset [81]. The same group reported that hemi- and homozygous loss-of-function variants in DSG-2 determine an early onset form of AC [82]. Desmoplakin (*DSP* gene, OMIM * 125647), a protein of the plakin cytolinker family, ligates PKP and plakoglobin in the intracellular compartment, thereby creating a connection between desmosomes and intermediate filaments [79]. Variants in DSP genes have been associated with a form of AC with extensive fibrosis and inflammatory activity in both ventricles. Desmin (*DES* gene, OMIM * 125660) represents the main component of the intermediate filaments: mutations in this gene can cause heterogenous phenotypes, including AC, dilated, and restrictive cardiomyopathies [79].

Desmosome proteins, area composita, gap junctions (mostly composed of connexin-43), and ion channels (including voltage-gated sodium channels) are strictly interconnected to preserve the structural and functional stability of the connexome [19,20,80]. Ryanodine receptor-2 (encoded by *RYR-2* gene, OMIM * 180902) regulates calcium release from the sarcoplasmic reticulum and is related to connexome function. Mutations in *RYR-2* genes have been strongly associated with catecholaminergic polymorphic ventricular tachycardia syndrome. Pathogenetic variants of phospholamban (*PLN* gene, OMIM * 172405), a structural component of the sarcoplasmic reticulum, determine severe forms of AC [79].

Behr et al. hypothesized that BrS could be the expression of an impaired RVOT conduction reserve, determined by reduced sodium channel currents, structural alterations, and inflammatory processes [26].

This complex interplay at the level of the gap junctions and connexome could potentially explain the structural and functional similarities between BrS and AC.

Some echocardiographic and CMR studies described reduced RV strain rate abnormalities both in BrS and AC compared to controls [83,84]. These observations support the hypothesis that BrS and AC could represent different phenotypic manifestations of a common spectrum of disorders.

Recently, many works described the importance of inflammatory and potential autoimmune processes in AC [85–87]. This evidence led to the emergent concept of inflammatory "hot phases" over the natural history of patients affected by AC and could suggest a common pathological mechanism involved in the pathogenesis of both conditions.

8. Future Perspectives: Genetics and Immune Modulation

Inflammation, apoptosis, and immune dysregulation play a crucial role in the pathogenesis of genetic cardiomyopathies and could significantly influence the prognosis of the patients [85–87]. Over recent years, some authors have reported positive outcomes in patients with genetically determined arrhythmogenic cardiomyopathies undergoing immunosuppressive treatment [88–91]. A case of recurrent myocarditis requiring multiple immunosuppressive regimes in a patient with a truncating variant of the demosplakin gene has been described in the literature [89]. Peretto et al. demonstrated possible beneficial effects of immunosuppression in patients with genetic cardiomyopathies and histological evidence of inflammatory infiltrates [91]. Interestingly, other authors reported an episode of giant cell-related fulminant myocarditis in a patient with a previous diagnosis of BrS [90]. Li et al. reported some BrS patients with arrhythmic storms presenting pathological uptake at 18-fluorodeoxyglucose positron emission tomography [92]. Moreover, the authors reported transitory improvement of the arrhythmic burden after prednisolone and hydroxychloroquine therapy. As previously described, inflammation and dysregulated immune response might represent common pathogenetic pathways both in BrS and genetic cardiomyopathies. Further prospective studies should evaluate the role of inflammation in the pathogenesis of the disease.

Another critical issue in BrS is the relatively low diagnostic yield of genetic testing. Monogenic models could not appropriately catch the complex interplay between ion channel dysfunction, pathological substrate, and acquired alterations (such as inflammation) in BrS. Recently, a polygenic risk score has been associated with worse outcomes in this population [59]. Further prospective studies are needed to validate the widespread use of these models in clinical practice.

9. Conclusions

Over the last twenty years, our knowledge of the pathophysiological mechanisms involved in BrS has dramatically increased, although many aspects still present significant areas of uncertainty. The emergent role of depolarization abnormalities together with the evidence of pathological voltages at EAM have suggested the presence of structural substrates in this condition. Novel echocardiographic and CMR techniques demonstrated the presence of subtle functional alterations in BrS. Histopathological and immunological data derived from serum and tissue samples of patients affected by BrS provided important information regarding the underlying disease substrate in terms of fibrosis, inflammatory processes, and the potential role of autoimmunity in this disease. Moreover, growing evidence of structural and functional similarities between BrS and AC has highlighted the continuous spectrum of pathological processes affecting the connexome complex. A better understanding of the pathological mechanisms involved in BrS pathogenesis could therefore improve prognostic evaluation. Moreover, the growing evidence of the role of inflammation and autoimmunity in this condition could potentially offer novel therapeutic strategies in BrS.

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Abbreviations

The following abbreviations are used in this manuscript:

BrS	Brugada syndrome
EPS	Electrophysiological study
EAM	Electroanatomic mapping
LP	Late potential
SA-ECG	Signal-average ECG
f-QRS	Fragmented QRS
RV	Right ventricle
LV	Left ventricle
RVOT	Right ventricular outflow tract
AV	Atrioventricular block
VT	Ventricular tachycardia
VF	Ventricular fibrillation
PVS	Programmed ventricular stimulation
RIMP	Right ventricular index of myocardial performance
RVEF	Right ventricular ejection fraction
CMR	Cardiac magnetic resonance
LGE	Late gadolinium enhancement
RVOT-FT	Right ventricular outflow tract-feature tracking
EMB	Endomyocardial biopsy

References

1. Brugada, P.; Brugada, J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. *J. Am. Coll. Cardiol.* **1992**, *20*, 1391–1396. [CrossRef] [PubMed]
2. Brugada, J.; Campuzano, O.; Arbelo, E.; Sarquella-Brugada, G.; Brugada, R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2018**, *72*, 1046–1059. [CrossRef] [PubMed]
3. Nademanee, K.; Veerakul, G.; Nimmannit, S.; Chaowakul, V.; Bhuripanyo, K.; Likittanasombat, K.; Tunsanga, K.; Kuasirikul, S.; Malasit, P.; Tansupasawadikul, S.; et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* **1997**, *96*, 2595–2600. [CrossRef] [PubMed]
4. Zeppenfeld, K.; Tfelt-Hansen, J.; de Riva, M.; Winkel, B.G.; Behr, E.R.; Blom, N.A.; Charron, P.; Corrado, D.; Dagres, N.; de Chillou, C.; et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur. Heart J.* **2022**, *43*, 3997–4126. [CrossRef]
5. Wilde, A.A.; Postema, P.G.; Di Diego, J.M.; Viskin, S.; Morita, H.; Fish, J.M.; Antzelevitch, C. The pathophysiological mechanism underlying Brugada syndrome. Depolarization versus repolarization. *J. Mol. Cell. Cardiol.* **2010**, *49*, 543–553. [CrossRef]
6. Sieira, J.; Dendramis, G.; Brugada, P. Pathogenesis and management of Brugada syndrome. *Nat. Rev. Cardiol.* **2016**, *13*, 744–756. [CrossRef]
7. Chen, Q.; Kirsch, G.E.; Zhang, D.; Brugada, R.; Brugada, J.; Brugada, P.; Potenza, D.; Moya, A.; Borggrefe, M.; Breithardt, G.; et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* **1998**, *392*, 293–296. [CrossRef]
8. Sarquella-Brugada, G.; Campuzano, O.; Arbelo, E.; Brugada, J.; Brugada, R. Brugada syndrome: Clinical and genetic findings. *Genet. Med.* **2016**, *18*, 3–12. [CrossRef]
9. Richards, S.; Aziz, N.; Bale, S.; Bick, D.; Das, S.; Gastier-Foster, J.; Grody, W.W.; Hegde, M.; Lyon, E.; Spector, E.; et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* **2015**, *17*, 405–424. [CrossRef]
10. Jordan, E.; Peterson, L.; Ai, T.; Asatryan, B.; Bronicki, L.; Brown, E.; Celeghin, R.; Edwards, M.; Fan, J.; Ingles, J.; et al. Evidence-Based Assessment of Genes in Dilated Cardiomyopathy. *Circulation* **2021**, *144*, 7–19. [CrossRef]
11. Peters, S.; Thompson, B.A.; Perrin, M.; James, P.; Zentner, D.; Kalman, J.M.; Vandenberg, J.I.; Fatkin, D. Arrhythmic Phenotypes Are a Defining Feature of Dilated Cardiomyopathy-Associated SCN5A Variants: A Systematic Review. *Circ. Genomic Precis. Med.* **2022**, *15*, E003432. [CrossRef] [PubMed]
12. Nademanee, K.; Veerakul, G.; Chandanamattha, P.; Chaothawee, L.; Ariyachaipanich, A.; Jirasirirojanakorn, K.; Likittanasombat, K.; Bhuripanyo, K.; Ngarmukos, T. Prevention of ventricular fibrillation episodes in brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. *Circulation* **2011**, *123*, 1270–1279. [CrossRef]
13. Letsas, K.P.; Efremidis, M.; Asvestas, D.; Vlachos, K.; Georgopoulos, S.; Tse, G.; Liu, T.; Bazoukis, G.; Sideris, A.; Baranchuk, A.; et al. Right Ventricular Outflow Tract Electroanatomical Abnormalities Predict Ventricular Fibrillation Inducibility in Brugada Syndrome. *Circ. Arrhythm. Electrophysiol.* **2018**, *11*, e005928. [CrossRef]
14. Frustaci, A.; Priori, S.G.; Pieroni, M.; Chimenti, C.; Napolitano, C.; Rivolta, I.; Sanna, T.; Bellocci, F.; Russo, M.A. Cardiac histological substrate in patients with clinical phenotype of Brugada syndrome. *Circulation* **2005**, *112*, 3680–3687. [CrossRef]
15. Nademanee, K.; Raju, H.; De Noronha, S.V.; Papadakis, M.; Robinson, L.; Rothery, S.; Makita, N.; Kowase, S.; Boonmee, N.; Vitayakritsirikul, V.; et al. Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome. *J. Am. Coll. Cardiol.* **2015**, *66*, 1976–1986. [CrossRef]
16. Pieroni, M.; Notarstefano, P.; Oliva, A.; Campuzano, O.; Santangeli, P.; Coll, M.; Nesti, M.; Carnevali, A.; Fraticelli, A.; Iglesias, A.; et al. Electroanatomic and Pathologic Right Ventricular Outflow Tract Abnormalities in Patients With Brugada Syndrome. *J. Am. Coll. Cardiol.* **2018**, *72*, 2747–2757. [CrossRef]
17. Mitroi, C.; García-Izquierdo, E.; García-Lunar, I.; Castro-Urda, V.; Toquero-Ramos, J.; Moñivas-Palomero, V.; Mingo-Santos, S.; Cavero, M.A.; Brugada, J.; Fernández-Lozano, I. Right ventricular function and dyssynchrony in Brugada syndrome: Highlighting the importance of the mechanical substrate in the right ventricular outflow tract. *Int. J. Cardiol.* **2021**, *333*, 233–238. [CrossRef]
18. Pappone, C.; Santinelli, V.; Mecarocci, V.; Tondi, L.; Ciconte, G.; Manguso, F.; Sturla, F.; Vicedomini, G.; Micaglio, E.; Anastasia, L.; et al. Brugada Syndrome: New Insights From Cardiac Magnetic Resonance and Electroanatomical Imaging. *Circ. Arrhythm. Electrophysiol.* **2021**, *14*, E010004. [CrossRef]
19. Moncayo-Arlandi, J.; Brugada, R. Unmasking the molecular link between arrhythmogenic cardiomyopathy and Brugada syndrome. *Nat. Rev. Cardiol.* **2017**, *14*, 744–756. [CrossRef]
20. Ben-Haim, Y.; Asimaki, A.; Behr, E.R. Brugada syndrome and arrhythmogenic cardiomyopathy: Overlapping disorders of the connexome? *Europace* **2021**, *23*, 653–664. [CrossRef]
21. Priori, S.G.; Wilde, A.A.; Horie, M.; Cho, Y.; Behr, E.R.; Berul, C.; Blom, N.; Brugada, J.; Chiang, C.E.; Huikuri, H.; et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes: Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm* **2013**, *10*, 1932–1963. [CrossRef] [PubMed]

22. Saura, D.; García-Alberola, A.; Carrillo, P.; Pascual, D.; Martínez-Sánchez, J.; Valdés, M. Brugada-like electrocardiographic pattern induced by fever. *Pacing Clin. Electrophysiol.* **2002**, *25*, 856–859. [CrossRef] [PubMed]
23. Kawada, S.; Morita, H.; Antzelevitch, C.; Morimoto, Y.; Nakagawa, K.; Watanabe, A.; Nishii, N.; Nakamura, K.; Ito, H. Shanghai Score System for Diagnosis of Brugada Syndrome: Validation of the Score System and System and Reclassification of the Patients. *JACC Clin. Electrophysiol.* **2018**, *4*, 724–730. [CrossRef] [PubMed]
24. Yan, G.X.; Antzelevitch, C. Cellular basis for the electrocardiographic J wave. *Circulation* **1996**, *93*, 372–379. [CrossRef]
25. Szél, T.; Antzelevitch, C. Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of brugada syndrome. *J. Am. Coll. Cardiol.* **2014**, *63*, 2037–2045. [CrossRef]
26. Behr, E.R.; Ben-Haim, Y.; Ackerman, M.J.; Krahn, A.D.; Wilde, A.A.M. Brugada syndrome and reduced right ventricular outflow tract conduction reserve: A final common pathway? *Eur. Heart J.* **2021**, *42*, 1073–1081. [CrossRef]
27. Gaita, F.; Cerrato, N.; Giustetto, C.; Martino, A.; Bergamasco, L.; Millesimo, M.; Barbonaglia, L.; Carvalho, P.; Caponi, D.; Saglietto, A.; et al. Asymptomatic Patients With Brugada ECG Pattern: Long-Term Prognosis From a Large Prospective Study. *Circulation* **2023**, *148*, 1543–1555. [CrossRef]
28. Nakano, Y.; Shimizu, W.; Ogi, H.; Suenari, K.; Oda, N.; Makita, Y.; Kajihara, K.; Hirai, Y.; Sairaku, A.; Tokuyama, T.; et al. A spontaneous Type 1 electrocardiogram pattern in lead V2 is an independent predictor of ventricular fibrillation in Brugada syndrome. *Europace* **2010**, *12*, 410–416. [CrossRef]
29. Sarkozy, A.; Chierchia, G.B.; Paparella, G.; Boussy, T.; De Asmundis, C.; Roos, M.; Henkens, S.; Kaufman, L.; Buyl, R.; Brugada, R.; et al. Inferior and lateral electrocardiographic repolarization abnormalities in brugada syndrome. *Circ. Arrhythm. Electrophysiol.* **2009**, *2*, 154–161. [CrossRef]
30. Kamakura, S.; Ohe, T.; Nakazawa, K.; Aizawa, Y.; Shimizu, A.; Horie, M.; Ogawa, S.; Okumura, K.; Tsuchihashi, K.; Sugi, K.; et al. Long-term prognosis of probands with brugada-pattern ST-elevation in leads V 1-V 3. *Circ. Arrhythm. Electrophysiol.* **2009**, *2*, 495–503. [CrossRef]
31. Kawata, H.; Morita, H.; Yamada, Y.; Noda, T.; Satomi, K.; Aiba, T.; Isobe, M.; Nagase, S.; Nakamura, K.; Kusano, K.F.; et al. Prognostic significance of early repolarization in inferolateral leads in Brugada patients with documented ventricular fibrillation: A novel risk factor for Brugada syndrome with ventricular fibrillation. *Heart Rhythm* **2013**, *10*, 1161–1168. [CrossRef] [PubMed]
32. Castro Hevia, J.; Antzelevitch, C.; Tornés Bárzaga, F.; Dorantes Sánchez, M.; Dorticós Balea, F.; Zayas Molina, R.; Quiñones Pérez, M.A.; Fayad Rodríguez, Y. Tpeak-Tend and Tpeak-Tend Dispersion as Risk Factors for Ventricular Tachycardia/Ventricular Fibrillation in Patients With the Brugada Syndrome. *J. Am. Coll. Cardiol.* **2006**, *47*, 1828–1834. [CrossRef] [PubMed]
33. Nagase, S.; Kataoka, N.; Morita, H.; Kamakura, T.; Ueoka, A.; Nakamura, T.; Oka, S.; Miyazaki, Y.; Wakamiya, A.; Nakajima, K.; et al. Demonstration of Arrhythmia Substrate-Associated Dispersion of Repolarization by Epicardial Unipolar Mapping in Brugada Syndrome. *JACC Clin. Electrophysiol.* **2024**, *10*, 1576–1588. [CrossRef]
34. Tada, T.; Kusano, K.F.; Nagase, S.; Banba, K.; Miura, D.; Nishii, N.; Watanabe, A.; Nakamura, K.; Morita, H.; Ohe, T. Clinical significance of macroscopic T-wave alternans after sodium channel blocker administration in patients with Brugada syndrome. *J. Cardiovasc. Electrophysiol.* **2008**, *19*, 56–61. [CrossRef]
35. Ikeda, T.; Sakurada, H.; Sakabe, K.; Sakata, T.; Takami, M.; Tezuka, N.; Nakae, T.; Noro, M.; Enjoji, Y.; Tejima, T.; et al. Assessment of Noninvasive Markers in Identifying Patients at Risk in the Brugada Syndrome: Insight Into Risk Stratification. *J. Am. Coll. Cardiol.* **2001**, *37*, 1628–1634. [CrossRef]
36. Takagi, M.; Yokoyama, Y.; Aonuma, K.; Aihara, N.; Hiraoka, M. Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with Brugada syndrome: Multicenter study in Japan. *J. Cardiovasc. Electrophysiol.* **2007**, *18*, 1244–1251. [CrossRef]
37. Junttila, M.J.; Brugada, P.; Hong, K.; Lizotte, E.; DEZutter, M.; Sarkozy, A.; Brugada, J.; Benito, B.; Perkiomaki, J.S.; Mäkikallio, T.H.; et al. Differences in 12-lead electrocardiogram between symptomatic and asymptomatic Brugada syndrome patients. *J. Cardiovasc. Electrophysiol.* **2008**, *19*, 380–383. [CrossRef]
38. Morita, H.; Kusano, K.F.; Miura, D.; Nagase, S.; Nakamura, K.; Morita, S.T.; Ohe, T.; Zipes, D.P.; Wu, J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation* **2008**, *118*, 1697–1704. [CrossRef]
39. Morita, H.; Watanabe, A.; Kawada, S.; Miyamoto, M.; Morimoto, Y.; Nakagawa, K.; Nishii, N.; Nakamura, K.; Ito, H. Identification of electrocardiographic risk markers for the initial and recurrent episodes of ventricular fibrillation in patients with Brugada syndrome. *J. Cardiovasc. Electrophysiol.* **2018**, *29*, 107–114. [CrossRef]
40. Babai Bigi, M.A.; Aslani, A.; Shahrzad, S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. *Heart Rhythm* **2007**, *4*, 1009–1012. [CrossRef]
41. Calò, L.; Giustetto, C.; Martino, A.; Sciarra, L.; Cerrato, N.; Marziali, M.; Rauzino, J.; Carlino, G.; de Ruvo, E.; Guerra, F.; et al. A New Electrocardiographic Marker of Sudden Death in Brugada Syndrome The S-Wave in Lead I. *J. Am. Coll. Cardiol.* **2016**, *67*, 1427–1440. [CrossRef] [PubMed]

42. Ragab, A.A.Y.; Houck, C.A.; van der Does, L.J.M.E.; Lanters, E.A.H.; Muskens, A.J.Q.M.; de Groot, N.M.S. Prediction of ventricular tachyarrhythmia in Brugada syndrome by right ventricular outflow tract conduction delay signs. *J. Cardiovasc. Electrophysiol.* **2018**, *29*, 998–1003. [CrossRef] [PubMed]
43. Sroubek, J.; Probst, V.; Mazzanti, A.; Delise, P.; Hevia, J.C.; Ohkubo, K.; Zorzi, A.; Champagne, J.; Kostopoulou, A.; Yin, X.; et al. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: A pooled analysis. *Circulation.* **2016**, *133*, 622–630. [CrossRef]
44. Pappone, C.; Ciconte, G.; Manguso, F.; Vicedomini, G.; Mecarocci, V.; Conti, M.; Giannelli, L.; Pozzi, P.; Borrelli, V.; Menicanti, L.; et al. Assessing the Malignant Ventricular Arrhythmic Substrate in Patients With Brugada Syndrome. *J. Am. Coll. Cardiol.* **2018**, *71*, 1631–1646. [CrossRef]
45. Alings, M.; Wilde, A. "Brugada" syndrome: Clinical data and suggested pathophysiological mechanism. *Circulation* **1999**, *99*, 666–673. [CrossRef]
46. Smits, J.P.; Eckardt, L.; Probst, V.; Bezzina, C.R.; Schott, J.J.; Remme, C.A.; Haverkamp, W.; Breithardt, G.; Escande, D.; Schulze-Bahr, E.; et al. Genotype-phenotype relationship in Brugada syndrome: Electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. *J. Am. Coll. Cardiol.* **2002**, *40*, 350–356. [CrossRef]
47. Lambiase, P.D.; Ahmed, A.K.; Ciaccio, E.J.; Brugada, R.; Lizotte, E.; Chaubey, S.; Ben-Simon, R.; Chow, A.W.; Lowe, M.D.; McKenna, W.J. High-density substrate mapping in brugada syndrome: Combined role of conduction and repolarization heterogeneities in arrhythmogenesis. *Circulation* **2009**, *120*, 106–117. [CrossRef]
48. Maury, P.; Rollin, A.; Sacher, F.; Gourraud, J.B.; Raczka, F.; Pasquié, J.L.; Duparc, A.; Mondoly, P.; Cardin, C.; Delay, M.; et al. Prevalence and prognostic role of various conduction disturbances in patients with the brugada syndrome. *Am. J. Cardiol.* **2013**, *112*, 1384–1389. [CrossRef]
49. Migliore, F.; Testolina, M.; Zorzi, A.; Bertaglia, E.; Silvano, M.; Leoni, L.; Bellin, A.; Basso, C.; Thiene, G.; Allocca, G.; et al. First-degree atrioventricular block on basal electrocardiogram predicts future arrhythmic events in patients with Brugada syndrome: A long-term follow-up study from the Veneto region of Northeastern Italy. *Europace* **2019**, *21*, 322–331. [CrossRef]
50. Rossi, A.; Giannoni, A.; Nesti, M.; Notarstefano, P.; Castiglione, V.; Solarino, G.; Teresi, L.; Mirizzi, G.; Russo, V.; Panchetti, L.; et al. Prognostic value of right ventricular refractory period heterogeneity in Type-1 Brugada electrocardiographic pattern. *Europace* **2023**, *25*, 651–659. [CrossRef]
51. Priori, S.G.; Gasparini, M.; Napolitano, C.; Della Bella, P.; Ottonelli, A.G.; Sassone, B.; Giordano, U.; Pappone, C.; Mascioli, G.; Rossetti, G.; et al. Risk stratification in brugada syndrome: Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J. Am. Coll. Cardiol.* **2012**, *59*, 37–45. [CrossRef] [PubMed]
52. Scheirlynck, E.; Van Malderen, S.; Motoc, A.; Lie, Ø.H.; de Asmundis, C.; Sieira, J.; Chierchia, G.B.; Brugada, P.; Cosyns, B.; Droogmans, S. Contraction alterations in Brugada syndrome; association with life-threatening ventricular arrhythmias. *Int. J. Cardiol.* **2020**, *299*, 147–152. [CrossRef] [PubMed]
53. Pappone, C.; Mecarocci, V.; Manguso, F.; Ciconte, G.; Vicedomini, G.; Sturla, F.; Votta, E.; Mazza, B.; Pozzi, P.; Borrelli, V.; et al. New electromechanical substrate abnormalities in high-risk patients with Brugada syndrome. *Heart Rhythm* **2020**, *17*, 637–645. [CrossRef] [PubMed]
54. Catalano, O.; Antonaci, S.; Moro, G.; Mussida, M.; Frascaroli, M.; Baldi, M.; Cobelli, F.; Baiardi, P.; Nastoli, J.; Bloise, R.; et al. Magnetic resonance investigations in Brugada syndrome reveal unexpectedly high rate of structural abnormalities. *Eur. Heart J.* **2009**, *30*, 2241–2248. [CrossRef]
55. Van Hoorn, F.; Campian, M.E.; Spijkerboer, A.; Blom, M.T.; Planken, R.N.; van Rossum, A.C.; de Bakker, J.M.; Wilde, A.A.; Groenink, M.; Tan, H.L. Scn5a mutations in brugada syndrome are associated with increased cardiac dimensions and reduced contractility. *PLoS ONE* **2012**, *7*, e42037. [CrossRef]
56. Gray, B.; Gnanappa, G.K.; Bagnall, R.D.; Femia, G.; Yeates, L.; Ingles, J.; Burns, C.; Puranik, R.; Grieve, S.M.; Semsarian, C.; et al. Relations between right ventricular morphology and clinical, electrical and genetic parameters in Brugada Syndrome. *PLoS ONE* **2018**, *13*, e0195594. [CrossRef]
57. Bastiaenen, R.; Cox, A.T.; Castelletti, S.; Wijeyeratne, Y.D.; Colbeck, N.; Pakroo, N.; Ahmed, H.; Bunce, N.; Anderson, L.; Moon, J.C.; et al. Late gadolinium enhancement in Brugada syndrome: A marker for subtle underlying cardiomyopathy? *Heart Rhythm* **2017**, *14*, 583–589. [CrossRef]
58. Isbister, J.C.; Gray, B.; Offen, S.; Yeates, L.; Naoum, C.; Medi, C.; Raju, H.; Semsarian, C.; Puranik, R.; Sy, R.W. Longitudinal assessment of structural phenotype in Brugada syndrome using cardiac magnetic resonance imaging. *Heart Rhythm O2* **2023**, *4*, 34–41. [CrossRef]
59. Kukavica, D.; Trancuccio, A.; Mazzanti, A.; Napolitano, C.; Morini, M.; Pili, G.; Memmi, M.; Gambelli, P.; Bloise, R.; Nastoli, J.; et al. Nonmodifiable Risk Factors Predict Outcomes in Brugada Syndrome. *J. Am. Coll. Cardiol.* **2024**, *84*, 2087–2098. [CrossRef]
60. Nademanee, K.; Chung, F.P.; Sacher, F.; Nogami, A.; Nakagawa, H.; Jiang, C.; Hocini, M.; Behr, E.; Veerakul, G.; Jan Smit, J.; et al. Long-Term Outcomes of Brugada Substrate Ablation: A Report from BRAVO (Brugada Ablation of VF Substrate Ongoing Multicenter Registry). *Circulation* **2023**, *147*, 1568–1578. [CrossRef]

61. Marra, M.P.; Leoni, L.; Bauce, B.; Corbetti, F.; Zorzi, A.; Migliore, F.; Silvano, M.; Rigato, I.; Tona, F.; Tarantini, G.; et al. Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy comparison of 3d standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance. *Circ. Arrhythm. Electrophysiol.* **2012**, *5*, 91–100. [CrossRef] [PubMed]
62. Casella, M.; Dello Russo, A.; Bergonti, M.; Catto, V.; Conte, E.; Sommariva, E.; Gasperetti, A.; Vettor, G.; Tundo, F.; Sicuso, R.; et al. Diagnostic Yield of Electroanatomic Voltage Mapping in Guiding Endomyocardial Biopsies. *Circulation* **2020**, *142*, 1249–1260. [CrossRef] [PubMed]
63. Brugada, J.; Pappone, C.; Berruezo, A.; Vicedomini, G.; Manguso, F.; Ciconte, G.; Giannelli, L.; Santinelli, V. Brugada Syndrome Phenotype Elimination by Epicardial Substrate Ablation. *Circ. Arrhythm. Electrophysiol.* **2015**, *8*, 1373–1381. [CrossRef]
64. Pappone, C.; Brugada, J.; Vicedomini, G.; Ciconte, G.; Manguso, F.; Saviano, M.; Vitale, R.; Cuko, A.; Giannelli, L.; Calovic, Z.; et al. Electrical Substrate Elimination in 135 Consecutive Patients with Brugada Syndrome. *Circ. Arrhythm. Electrophysiol.* **2017**, *10*, e005053. [CrossRef]
65. Talib, A.K.; Takagi, M.; Shimane, A.; Nakano, M.; Hayashi, T.; Okajima, K.; Kentaro, M.; Fukada, K.; Kowase, S.; Kurosaki, K.; et al. Efficacy of Endocardial Ablation of Drug-Resistant Ventricular Fibrillation in Brugada Syndrome. *Circ. Arrhythm. Electrophysiol.* **2018**, *11*, e005631. [CrossRef]
66. Cheniti, G.; Haissaguerre, M.; Dina, C.; Kamakura, T.; Duchateau, J.; Sacher, F.; Racine, H.P.; Surget, E.; Simonet, F.; Gourraud, J.B.; et al. Left Ventricular Abnormal Substrate in Brugada Syndrome. *JACC Clin. Electrophysiol.* **2023**, *9*, 2041–2051. [CrossRef]
67. Coronel, R.; Casini, S.; Koopmann, T.T.; Wilms-Schopman, F.J.; Verkerk, A.O.; de Groot, J.R.; Bhuiyan, Z.; Bezzina, C.R.; Veldkamp, M.W.; Linnenbank, A.C.; et al. Right ventricular fibrosis and conduction delay in a patient with clinical signs of Brugada syndrome: A combined electrophysiological, genetic, histopathologic, and computational study. *Circulation* **2005**, *112*, 2769–2777. [CrossRef]
68. Santangeli, P.; Hamilton-Craig, C.; Dello Russo, A.; Pieroni, M.; Casella, M.; Pelargonio, G.; Di Biase, L.; Smaldone, C.; Bartoletti, S.; Narducci, M.L.; et al. Imaging of scar in patients with ventricular arrhythmias of right ventricular origin: Cardiac magnetic resonance versus electroanatomic mapping. *J. Cardiovasc. Electrophysiol.* **2011**, *22*, 1359–1366. [CrossRef]
69. Chatterjee, D.; Pieroni, M.; Fatah, M.; Charpentier, F.; Cunningham, K.S.; Spears, D.A.; Chatterjee, D.; Suna, G.; Bos, J.M.; Ackerman, M.J.; et al. An autoantibody profile detects Brugada syndrome and identifies abnormally expressed myocardial proteins. *Eur. Heart J.* **2020**, *41*, 2878–2890. [CrossRef]
70. Corrado, D.; van Tintelen, P.J.; McKenna, W.J.; Hauer, R.N.W.; Anastastakis, A.; Asimaki, A.; Basso, C.; Bauce, B.; Brunckhorst, C.; Bucciarelli-Ducci, C.; et al. Arrhythmogenic right ventricular cardiomyopathy: Evaluation of the current diagnostic criteria differential diagnosis. *Eur. Heart J.* **2020**, *41*, 1414–1427. [CrossRef]
71. Del Franco, A.; Ruggieri, R.; Pieroni, M.; Ciabatti, M.; Zocchi, C.; Biagioni, G.; Tavanti, V.; Del Pace, S.; Leone, O.; Favale, S.; et al. Atlas of Regional Left Ventricular Scar in Nonischemic Cardiomyopathies: Substrates and Etiologies. *JACC Adv.* **2024**, *3*, 101214. [CrossRef] [PubMed]
72. Santangeli, P.; Dello Russo, A.; Pieroni, M.; Casella, M.; Di Biase, L.; Burkhardt, J.D.; Sanchez, J.; Lakkireddy, D.; Carbucicchio, C.; Zucchetti, M.; et al. Fragmented and delayed electrograms within fibrofatty scar predict arrhythmic events in arrhythmogenic right ventricular cardiomyopathy: Results from a prospective risk stratification study. *Heart Rhythm* **2012**, *9*, 1200–1206. [CrossRef] [PubMed]
73. Marcus, F.I.; McKenna, W.J.; Sherrill, D.; Basso, C.; Bauce, B.; Bluemke, D.A.; Calkins, H.; Corrado, D.; Cox, M.G.; Daubert, J.P.; et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/Dysplasia: Proposed modification of the task force criteria. *Circulation* **2010**, *121*, 1533–1541. [CrossRef]
74. Santangeli, P.; Pieroni, M.; Dello Russo, A.; Casella, M.; Pelargonio, G.; Macchione, A.; Camporeale, A.; Smaldone, C.; Bartoletti, S.; Di Biase, L.; et al. Noninvasive diagnosis of electroanatomic abnormalities in arrhythmogenic right ventricular cardiomyopathy. *Circ. Arrhythm. Electrophysiol.* **2010**, *3*, 632–638. [CrossRef] [PubMed]
75. Corrado, D.; Nava, A.; Buja, G.; Martini, B.; Fasoli, G.; Oselladore, L.; Turrini, P.; Thiene, G. Familial cardiomyopathy underlies syndrome of right bundle branch block, ST segment elevation and sudden death. *J. Am. Coll. Cardiol.* **1996**, *27*, 443–448. [CrossRef]
76. Corrado, D.; Basso, C.; Buja, G.; Nava, A.; Rossi, L.; Thiene, G. Right bundle branch block, right precordial st-segment elevation, and sudden death in young people. *Circulation* **2001**, *103*, 710–717. [CrossRef]
77. Letsas, K.P.; Efremidis, M.; Weber, R.; Korantzopoulos, P.; Protonotarios, N.; Prappa, E.; Kounas, S.P.; Evagelidou, E.N.; Xydonas, S.; Kalusche, D.; et al. Epsilon-like waves and ventricular conduction abnormalities in subjects with type 1 ECG pattern of Brugada syndrome. *Heart Rhythm* **2011**, *8*, 874–878. [CrossRef]
78. Wilde, A.A.M.; Amin, A.S. Clinical Spectrum of SCN5A Mutations: Long QT Syndrome, Brugada Syndrome, and Cardiomyopathy. *JACC Clin. Electrophysiol.* **2018**, *4*, 569–579. [CrossRef]
79. Gerull, B.; Brodehl, A. Insights Into Genetics and Pathophysiology of Arrhythmogenic Cardiomyopathy. *Curr. Heart Fail. Rep.* **2021**, *18*, 378–390. [CrossRef]

80. Agullo-Pascual, E.; Cerrone, M.; Delmar, M. Arrhythmogenic cardiomyopathy and Brugada syndrome: Diseases of the connexome. *FEBS Lett.* **2014**, *588*, 1322–1330. [CrossRef]
81. Brodehl, A.; Weiss, J.; Debus, J.D.; Stanasiuk, C.; Klauke, B.; Deutsch, M.A.; Fox, H.; Bax, J.; Ebbinghaus, H.; Gärtner, A.; et al. A homozygous DSC2 deletion associated with arrhythmogenic cardiomyopathy is caused by uniparental isodisomy. *J. Mol. Cell. Cardiol.* **2020**, *141*, 17–29. [CrossRef] [PubMed]
82. Brodehl, A.; Meshkov, A.; Myasnikov, R.; Kiseleva, A.; Kulikova, O.; Klauke, B.; Sotnikova, E.; Stanasiuk, C.; Divashuk, M.; Pohl, G.M.; et al. Hemi- and Homozygous Loss-of-Function Mutations in DSG2 (Desmoglein-2) Cause Recessive Arrhythmogenic Cardiomyopathy with an Early Onset. *Int. J. Mol. Sci.* **2021**, *22*, 3786. [CrossRef]
83. Iacoviello, M.; Forleo, C.; Puzzovivo, A.; Nalin, I.; Guida, P.; Anaclerio, M.; Marangelli, V.; Sorrentino, S.; Monitillo, F.; Ciccone, M.M.; et al. Altered two-dimensional strain measures of the right ventricle in patients with Brugada syndrome and arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Eur. J. Echocardiogr.* **2011**, *12*, 773–781. [CrossRef]
84. Heermann, P.; Fritsch, H.; Koopmann, M.; Sporns, P.; Paul, M.; Heindel, W.; Schulze-Bahr, E.; Schülke, C. Biventricular myocardial strain analysis using cardiac magnetic resonance feature tracking (CMR-FT) in patients with distinct types of right ventricular diseases comparing arrhythmogenic right ventricular cardiomyopathy (ARVC), right ventricular outflow-tract tachycardia (RVOT-VT), and Brugada syndrome (BrS). Clinical Research in Cardiology. *Clin. Res. Cardiol.* **2019**, *108*, 1147–1162. [CrossRef]
85. Bariani, R.; Cipriani, A.; Rizzo, S.; Celeghin, R.; Bueno Marinas, M.; Giorgi, B.; De Gaspari, M.; Rigato, I.; Leoni, L.; Zorzi, A.; et al. "Hot phase" clinical presentation in arrhythmogenic cardiomyopathy. *Europace* **2021**, *23*, 907–917. [CrossRef]
86. Peretto, G.; Casella, M.; Merlo, M.; Benedetti, S.; Rizzo, S.; Cappelletto, C.; Di Resta, C.; Compagnucci, P.; De Gaspari, M.; Dello Russo, A.; et al. Inflammation on Endomyocardial Biopsy Predicts Risk of MACE in Undefined Left Ventricular Arrhythmogenic Cardiomyopathy. *JACC Clin. Electrophysiol.* **2023**, *9*, 951–961. [CrossRef]
87. Caforio, A.L.P.; Re, F.; Avella, A.; Marcolongo, R.; Baratta, P.; Seguso, M.; Gallo, N.; Plebani, M.; Izquierdo-Bajo, A.; Cheng, C.Y.; et al. Evidence from Family Studies for Autoimmunity in Arrhythmogenic Right Ventricular Cardiomyopathy: Associations of Circulating Anti-Heart and Anti-Intercalated Disk Autoantibodies with Disease Severity and Family History. *Circulation* **2020**, *141*, 1238–1248. [CrossRef]
88. Bassetto, G.; Angriman, F.; Gava, C.P.L.D.; Paldino, A.; Perotto, M.; Bordignon, L.; Gigli, M.; Ferro, M.D.; Massa, L.; Altinier, A.; et al. Hot Phases Cardiomyopathy: Pathophysiology, Diagnostic Challenges, and Emerging Therapies. *Curr. Cardiol. Rep.* **2025**, *27*, 11. [CrossRef]
89. McColl, H.; Cordina, R.; Lal, S.; Parker, M.; Hunyor, I.; Medi, C.; Gray, B. Recurrent immunosuppressive-responsive myocarditis in a patient with desmoplakin cardiomyopathy: A case report. *Eur. Heart J. Case Rep.* **2024**, *8*, ytae129. [CrossRef]
90. Kuroki, K.; Yamamoto, M.; Sato, A. Successful treatment of life-threatening giant cell myocarditis in a patient with Brugada syndrome, controlled through dual ablation procedures and immunosuppressive therapy. *Eur. Heart J. Cardiovasc. Imaging* **2024**, *25*, E97. [CrossRef]
91. Peretto, G.; De Luca, G.; Villatore, A.; Di Resta, C.; Sala, S.; Palmisano, A.; Vignale, D.; Campochiaro, C.; Lazzeroni, D.; De Gaspari, M.; et al. Multimodal Detection and Targeting of Biopsy-Proven Myocardial Inflammation in Genetic Cardiomyopathies: A Pilot Report. *JACC Basic Transl. Sci.* **2023**, *8*, 755–765. [CrossRef] [PubMed]
92. Li, A.; Tung, R.; Shivkumar, K.; Bradfield, J.S. Brugada syndrome—Malignant phenotype associated with acute cardiac inflammation? *HeartRhythm Case Rep.* **2017**, *3*, 384–388. [CrossRef] [PubMed]